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Child With Wilms' Tumor and von Willebrand Disease at Diagnosis and Apparent Complete Response to Chemotherapy After Multiple Relapses

Ronald D. Barr, MBChB, MD, Andrea Winthrop, MD, Derek deSa, MBBS, PhD, Gerald Gill, MD, Jacob Langer, MD, Peter Fitzgerald, MD, and Anthony C. Whitton, MBBS

Key words: nephroblastoma, relapse, chemotherapy, remission, von Willebrand disease

Ronald Barr, MD (Pediatric Oncologist)

CR presented, as a 3¾-year-old girl in October 1989, with a large mass (measuring 11 × 12 × 13 cm on CT scan) in the right kidney. Approximately 2 years earlier she had undergone renal ultrasonography (for investigation of recurrent urinary tract infection) and no structural abnormalities were detected. The only unusual feature was the identification of acquired von Willebrand disease (VWD) which was demonstrated on routine pre-operative assessment in the absence of a hemorrhagic diathesis. Surgery was performed after the administration of DDAVP (to which a prior response had been demonstrated; see Table I) and cryoprecipitate. Dr. Winthrop, please describe your operative findings.

Andrea Winthrop, MD (Pediatric Surgeon)

At nephrectomy, the mass was essentially replacing the right kidney but was mobile and did not involve the liver. The tumor capsule was intact and dissection was accomplished outside Gerota's fascia with complete resection of the tumor and residual kidney. An estimated 400 ml of blood loss reflected the need to repair the inferior vena cava.

Dr. Barr. The coagulation abnormality, characterized as type 1 VWD, resolved following tumor resection (Table I). Dr. deSa, will you tell us about the histopathology?

Derek deSa, MBBS (Pediatric Pathologist)

The mass proved to be a Stage II Wilms' tumor of typical favorable histology (Fig. 1). There was some vascular invasion but the main renal vein was clear. A pseudocapsule was present. There was no evidence of anaplasia or persistent nephrogenic rests. Regional lymph nodes were free of tumor.

Dr. Barr. This child received double agent chemotherapy (vincristine and actinomycin D) for 15 months, according to regimen K of the NWTS 3 study [1]. No radiotherapy was given and she completed the protocol in January 1991, having experienced minimal morbidity during treatment. Repeated abdominal ultrasound examinations and chest radiography revealed no evidence of recurrent disease until February 1992, although she remained asymptomatic. Dr. Gill, will you show us the relevant radiological features?

Gerald Gill, MD (Pediatric Radiologist)

A solitary mass was identified in the right upper retroperitoneum and confirmed as intrahepatic by CT scan and hepatic arteriography (Figs. 2, 3).

Dr. Barr. With current multimodal therapy, children who have newly diagnosed Stage II nephroblastoma (Wilms' tumor) enjoy an approximately 95% likelihood of being alive 2 years later [2]. However, for Wilms' tumor patients taken together who experience a relapse of

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TABLE I. Studies of Hemostasis*

Index	Time 1	Time 2	Time 3
Bleeding time (min)	7	5 1/2	—
P.T.T. (sec)	56[a]	48[a]	41
Factor VIII-C (u/ml)	0.34[a]	0.60	1.20
Factor VIII-Ag (u/ml)	0.59	0.60	1.20
Factor VIII-RCF (u/ml)	0.29[a]	0.77	1.15
Factor VIII multimers	Normal	Increased HMW	Normal

*Time 1 = pre-operative, pre-DDAVP; Time 2 = pre-operative, 1 hour post-DDAVP; Time 3 = two weeks post-operative; C = coagulant activity; Ag = antigen; RCF = ristocetin co-factor; HMW = multimers of high molecular weight.
[a] = abnormal.

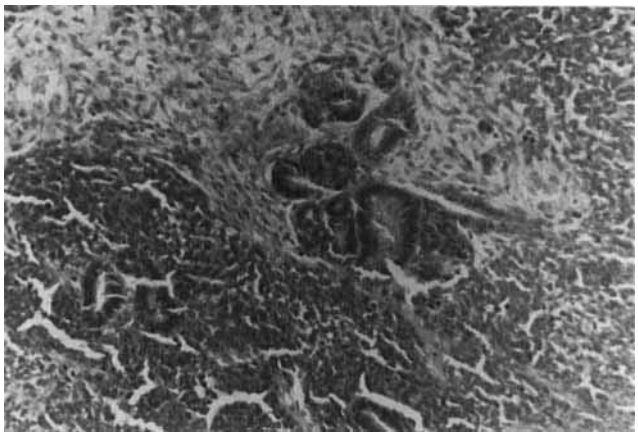

Fig. 1. Photomicrograph of a representative area from the nephrectomy specimen showing Wilms' tumor with features consistent with favorable histology.

this disease after such treatment, the prospect for long-term survival is considerably less, averaging 30% at 3 more years (the interval within which 95% of deaths occur) [3]. Predictive determinants of post-relapse survival have been analyzed in detail [3]. These include tumor histology, initial therapy, length of first remission, and site of relapse. Recurrence in the liver carries a particularly dismal prognosis, with a 14% survival rate at 4 years after relapse [4]. Dr. Langer, please describe your findings at the second surgical exploration.

Jacob Langer, MD (Pediatric Surgeon)

CR underwent right hepatic lobectomy, with no preoperative evidence of recurrent, acquired VWD. No other site of disease was identified. Blood loss was approximately 500 ml and she made a prompt, uncomplicated recovery.

Dr. deSa. The surgical specimen contained a pseudo-encapsulated, single mass (6 cm diameter) which consisted of Wilms' tumor having favorable histology, as before. The lines of resection were free of involvement.

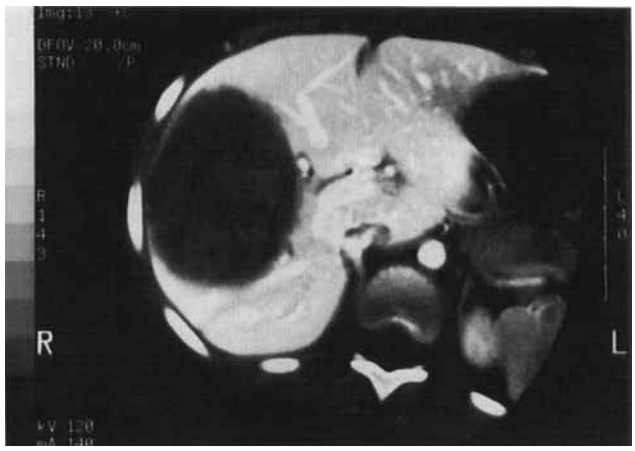

Fig. 2. Computerized axial tomography revealing an intrahepatic mass at the time of first recurrence of disease. Contrast medium delivered through the superior mesenteric artery.

Dr. Barr. No adjuvant treatment was given, in view of prior experience with Wilms' tumor recurring in the liver [4]. While remaining clinically entirely well, this child demonstrated stable, postoperative, radiological abnormalities in the region of the right side of the liver until September 1992 when CT scan and ultrasonography revealed a mass (4 cm diameter).

Dr. Gill. Magnetic resonance imaging revealed that the mass was extending superiorly from the right renal bed into the adjacent liver (Fig. 4). Chest radiography was normal.

Dr. Barr. CR underwent another laparotomy. Dr. Winthrop, will you please describe your experience on that occasion.

Dr. Winthrop. Sub-total resection of the mass was accomplished. The tumor was adherent to the abdominal wall and right hemi-diaphragm. Direct visualization confirmed that the mass was extending from the right renal bed into the liver. Estimated blood loss was 1,400 ml. Again, no other site of disease was identified.

Dr. deSa. Histological assessment of the resected material confirmed the presence of recurrent Wilms' tumor without any features of anaplasia. There was microscopic evidence of hepatic invasion. The tumor formed a distinct compression pseudo-capsule separating it from the liver tissue (Fig. 5).

Dr. Barr. Because of the presence of gross residual disease, it was decided to administer adjuvant chemotherapy. She received doxorubicin at 20 mg per m^2 per day on 3 consecutive days. This regimen was repeated 3 weeks later. Radiological re-examination demonstrated a reduction in the size of the mass by comparison with that detected in the immediate postoperative period. Accordingly, further chemotherapy was intensified. In addition to a further 3 days of doxorubicin (at 15 mg per m^2 per

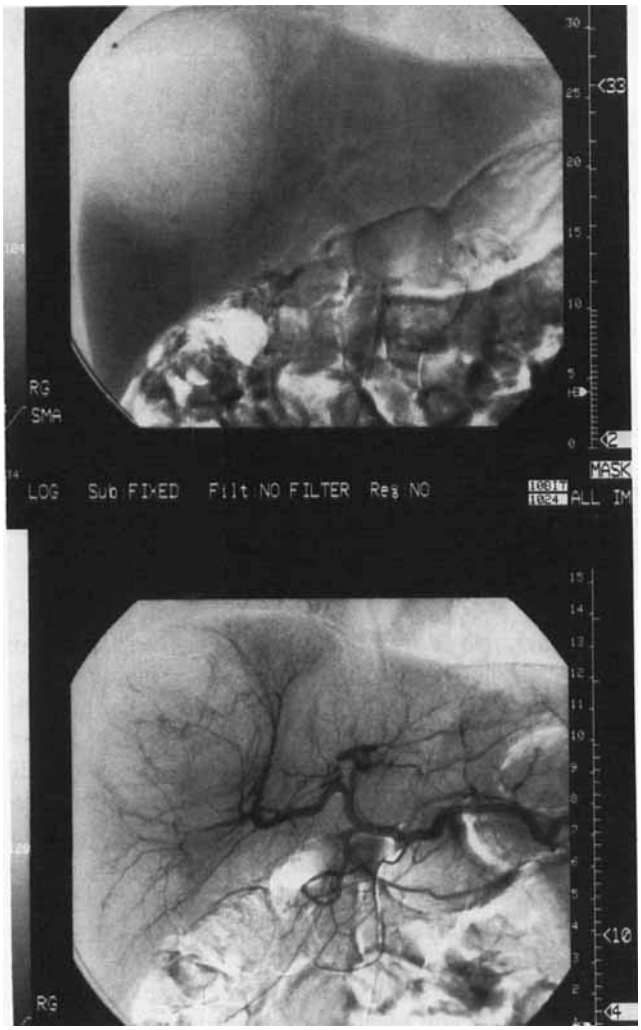

Fig. 3. Hepatic arteriography at the time of first recurrence of disease, demonstrating a tumor associated circulation and distortion of the normal vascular anatomy. Lower image: arterial phase; upper image: venous phase.

Fig. 4. Magnetic resonance imaging. Conventional spin echo with T2 weighted image revealing the second recurrence of disease—a mass extending from the right renal fossa into the adjacent liver.

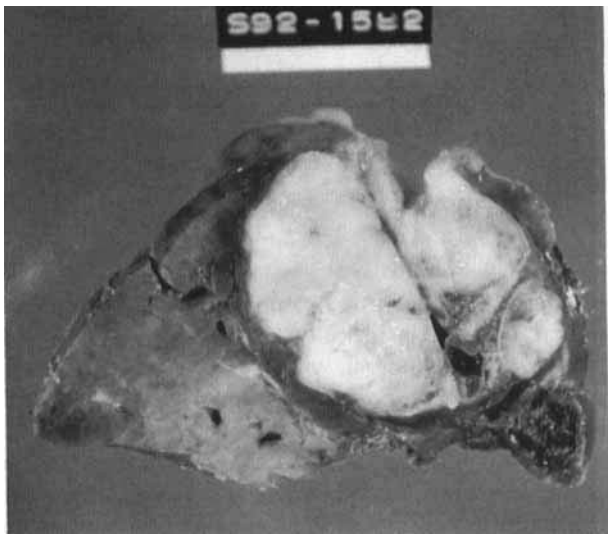

Fig. 5. Gross appearance of the specimen removed at the third laparotomy.

day) she was given ifosfamide (1,800 mg per m^2 per day for 5 days) with carboplatin 175 mg per m^2 on the first day. This regimen was repeated 1 month later on recovery from pancytopenia.

The appearances on abdominal ultrasonography and CT scan remained unchanged during triple agent therapy. Since the child was clinically well and the chest radiograph still normal, a "second (actually fourth!) look" laparotomy was performed in February 1993. Dr. Fitzgerald, what was achieved surgically?

Peter Fitzgerald, MD (Pediatric Surgeon)

On this occasion, complete resection of a dark-brown, pseudo-encapsulated mass (measuring 4 × 2 × 1 cm) from the previous tumor bed was possible. Careful surgical examination of the abdomen failed to uncover any other focus of disease. Blood loss from the procedure was negligible.

Dr. deSa. On microscopic examination, this was shown to consist almost entirely of necrotic material and organizing hemorrhage. The only viable tissue was a small component of normal liver (Fig. 6).

Dr. Barr. It was decided to administer radiotherapy to the site of previous tumor involvement and to proceed to

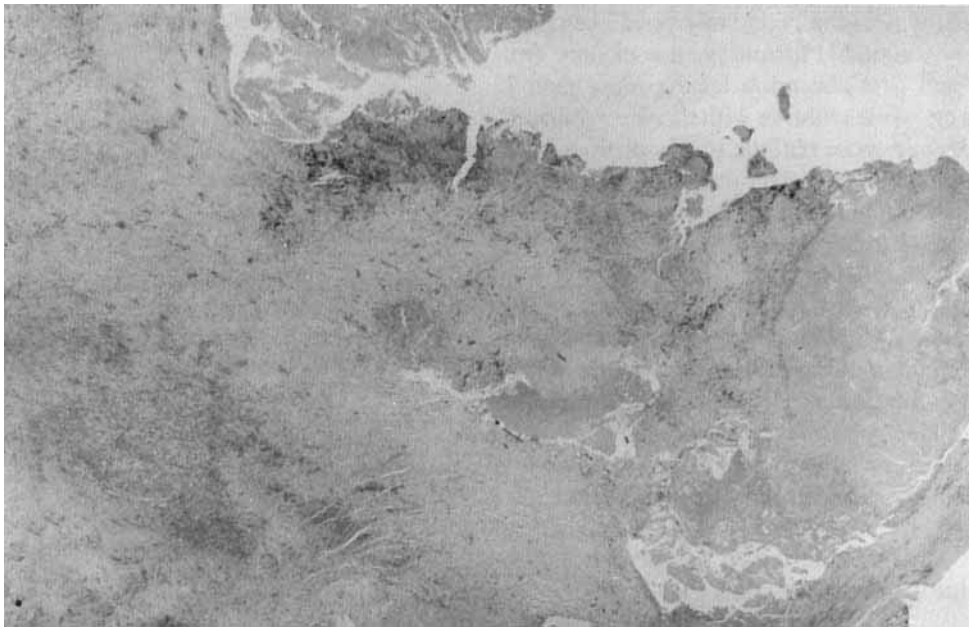

Fig. 6. Photomicrograph of a representative area from the pseudo-encapsulated mass showing only fibrotic tissue and foci of necrosis.

further chemotherapy thereafter. Dr. Whitton, will you kindly provide us with an account of your management?

Anthony Whitton, MBBS (Pediatric Radiation Oncologist)

A midplane dose of 1,000 cGy was delivered in six equal daily fractions over 8 days to 13.5 × 20 cm anterior and posterior parallel-opposed fields covering the original tumor area. A further mid-plane dose of 1,000 cGy was given in six fractions over 8 days to 13.5 × 16 cm parallel-opposed fields covering the area of tumor recurrence. The treatment ports crossed the midline to cover the adjacent vertebrae in order to avoid scoliosis. The dose given may cause impairment of growth of these vertebrae but should be within tolerance for the liver and other normal tissues included in the fields. The child tolerated this treatment well, with no acute toxicity.

Dr. Barr. Since the cumulative dose of doxorubicin was 225 mg per m^2, it was agreed that etoposide be substituted. This was given at 100 per m^2 per day for 5 days, with ifosfamide and carboplatin as before. Mesna was used for uroprotection as previously. Three such cycles were administered at intervals of 4 weeks. A combination of dexamethasone and ondansetron was given as very effective anti-emetic therapy and G-CSF was administered following chemotherapy until recovery of the neutrophil count. Two admissions (of 5 and 10 days) were required for the management of fever and neutropenia. Red blood cell transfusions were needed only on two occasions but 21 units of platelets were required (in a total of four occasions). Mucositis was not a major problem. The treatment was concluded in June 1993.

Two unusual features distinguished this child at the time of original diagnosis. First, availability of a normal renal ultrasonogram establishes that there was no gross tumor 2 years before clinical manifestation. Second, acquired von Willebrand disease (VWD) demands intervention to limit blood loss during nephrectomy. This coagulopathy may be more commonly associated with Wilms' tumor than is widely supposed [5]. The pathogenesis of acquired VWD in this context is uncertain, although specific inhibitors of von Willebrand factor have not been found in patients with Wilms' tumor [5], and the coagulopathy always resolves on treatment of the neoplasm [5]. Nevertheless, the use of DDAVP pre-operatively is a logical recommendation [6]. Curiously, there was no recurrence of acquired VWD in this child when her Wilms' tumor relapsed. There appears to be no comparable experience in the medical literature.

The nature of the relapses in this case may be open to debate. While the radiological and surgical findings, immediately prior to and during the third and fourth laparotomies respectively, are compatible with local recurrence of Wilms' tumor in the right renal bed, and contiguous involvement of the liver, the features of the first relapse (including the histological observations) are consistent with a solitary hepatic metastasis. This distinction may have been (and may still be) important in prognostication.

Of the four main determinants of outcome following

relapse, this child was in the "relatively good" category for three; namely, favorable histology, use of only two drugs initially, and first remission lasting more than 1 year [3]. However, while children with disease *recurrent* in the liver have a very poor outlook [4] (as distinct from children who have hepatic involvement at diagnosis) [7], those with local abdominal relapses may have a prospect of long-term survival that exceeds 85%, if they had not received previous radiotherapy [3].

Adjuvant therapy following surgical intervention for relapsed Wilms' tumor is generally recommended. The choice of doxorubicin, ifosfamide, and carboplatin in this child was based on reports of responsiveness to these or related drugs in children with recurrent disease [3,8–12]. They seem to have been effective, since no residual tumor was found in the resected specimen after her last operation (Fig. 6). It could be argued that the radiation therapy given thereafter contributed to the continuing control of the local disease, a point that must remain moot.

Only a small minority of children who receive current treatment for Wilms' tumor will suffer a recurrence. The prospect for prolonged, post-relapse survival is highly variable and, to a considerable degree, predictable. Use of a multi-modality approach to the management of recurrent Wilms' tumor, incorporating the aggressive administration of several drugs which have proven activity in this circumstance, offers the possibility of cure for these unfortunate children.

In summary, this child is noteworthy for three reasons: first, the coincidence of von Willebrand disease and Wilms' tumor; second, long term control of a large metachronous metastasis in the liver; and third, what appears to be successful elimination by chemotherapy of active disease in a recurrent tumor bed lesion.

ADDENDUM

The patient remains free of disease twenty-two months since the completion of all therapy.

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SERIES EDITOR'S NOTE[1]

Erik A. von Willebrand (1870–1939) was a Finnish physician who described the bleeding disorder that carries his name. It was the first familial hemorrhagic disease identified after hemophilia. He apparently became aware of it while serving as a doctor in Mariehamn, the capital of the Åland Islands, where it was known as "Alandic hemorrhagic disease." Years later, a child from those islands was referred to Helsinki, where Dr. von Willebrand had since relocated. His exhaustive investigations of the family pedigree identified the disease as being familial, dominant in inheritance pattern, and affecting both sexes equally.

Dr. von Willebrand had a long and distinguished career at Helsinki University, first in the Department of Physiology and later in the Department of Medicine. He

[1]Based largely on data in Firkin BG, Whitworth JA: "Dictionary of Medical Eponyms." Park Ridge, NJ: Parthenon Publishing Group, 1987.

contributed much to the literature both in physiology and medicine, reflecting his scientific breadth that ranged from the physiologic effects of the *sauna* (Finnish word) to the medical management of diabetes by diet control.

Biographers agree he was a modest, retiring person not given to self-aggrandizement. His perceptive studies in science are nonetheless remembered through the eponymic syndrome.

Finnish is a Finno-Ugric language (*Ugrian* from old Russian *Ugre* = Hungarian) of unusual complexity. Sharing features with Hungarian, it is unlike any of the Indo-European languages. It instead appears to be a derivative of unique dialects originating in the northern reaches of Asia and carried West by invaders.